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THE JOHN CREAR... REMOVED

THE PHYSIOLOGICAL RESPONSES OF THE CIRCULATION TO ANAEMIA*

This paper is concerned with a description of the cardiovascular changes which occur in anaemia. Particular emphasis will be placed on the time relationships of these changes during the development of the anaemia and during treatment. The various mechanisms that different investigators have considered to be responsible for the elevated cardiac output regularly observed in anaemia also will be discussed.

HAEMOGLOBIN AND CARDIAC OUTPUT

There has been some variation noted in the level of haemoglobin at which the cardiac output becomes elevated. The available evidence indicates that these variable findings are, at least in part, due to the rate at which the anaemia occurs and/or the accompanying level of the blood volume.

Investigations of chronic anaemia** indicate that the cardiac output becomes elevated when the haemoglobin is reduced to about 7 gm./100 cc. blood.[1] In these cases the blood volume is reduced.[1] The sequential relationships between haemoglobin and cardiac output have been studied in dogs in which an anaemia was produced slowly by daily venesections.[2] When the haemoglobin reached approximately 7 gm./100 cc. blood, the cardiac output began to rise, and at this time the daily venesections were stopped. Following the final venesection, the cardiac output continued to rise to a maximum over the course of 1 to 7 days independent of any further significant changes in haemoglobin and total blood volume.

Elevations in cardiac output have been observed in man with less marked degrees of anaemia when this state has occurred rapidly as a result of severe haemorrhage,[3] especially when the blood volume was reconstituted by replacement therapy with plasma or plasma substitutes.[4] However, this does not regularly occur in anaesthetized dogs made rapidly anaemic by a blood for plasma[5] or plasma substitute[6] exchange. In these animal experiments the haemoglobin fell to 7 gm. per cent before the cardiac output rose, and, as in the case of slowly produced anaemia in dogs, once the cardiac output elevation was initiated, it continued to a maximum independent of further decreases in haemoglobin.

When the haemoglobin concentration is diluted in normal animals by infusions of plasma or plasma substitute at a rate of 0.5 cc./kilo/minute, a rise in cardiac output is observed as the haemoglobin concentration is reduced.[7] In this circumstance the elevation in cardiac output would not seem to be the result of infusion per se, for infusions of similar volumes of normal whole blood at a similar rate do not elevate the cardiac output.[8] It is to be noted, however, that when such infusions are given at a more rapid rate, elevations in cardiac output do occur.[9]

The fact that in chronic anaemia the cardiac output is elevated in the presence of a decreased blood volume indicates that a reduction in the capacity of the vascular bed must occur. As will be pointed out in the subsequent two sections, this reduction appears to be largely on the venous side of the circulation.

PERIPHERAL CIRCULATION

When the cardiac output is elevated, the calculated total peripheral resistance

$$\text{(T.P.R.} = \frac{\text{mean arterial blood pressure}}{\text{cardiac output}}\text{)}$$

is reduced, indicating a peripheral vasodilatation.[2] However, studies of regional blood flow indicate that this is not a generalized response. Plethysmographic studies of the circulation in the extremities reveal that the muscle blood flow is increased and the skin blood flow reduced.[10] The cerebral blood flow is elevated.[11] The renal

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**This term is used to include not only the various dyshaemopoetic and haemolytic types but also the anaemia which follows repeated loss of small volumes of blood. These anaemias are generally slow in development and of long duration.

blood flow is diminished,[12] and there is evidence that vasoconstriction of the afferent arterioles is more pronounced than that of the efferent arterioles. Although the blood flow through the kidneys is reduced, the amount of plasma presented to the glomerulus is nearly normal as a result of the decreased haematocrit.

Prior to the development of the high cardiac output, muscle blood flow is within normal limits, and the skin blood flow is reduced.[2]

BLOOD VOLUME AND VENOUS PRESSURE

Sharpey-Schafer[13] found a reduced total blood volume, a high cardiac output, and an elevated right atrial pressure in patients with chronic and post-haemorrhagic anaemia. On the basis of these findings plus the evidence of peripheral arteriolar dilatation, he postulated the existence of a venomotor mechanism which decreased the capacity of the vascular bed and increased the venous filling pressure. Sharpey-Schaefer considered that the increased filling pressure brought about the increased cardiac output in keeping with Starling's Law of the Heart. In studies on dogs[2] made anaemic by daily venesections, the right atrial pressure was observed to be elevated and the total blood volume reduced when the cardiac output was high. However, the initial elevation in right atrial pressure occurred several days before the initial rise in cardiac output. It was argued that, if the rise in cardiac output were the result of an increased right atrial pressure, a coincident rise would have been noted in both. It was concluded from this study that the elevated right atrial pressure may represent, as Sharpey-Schafer pointed out,[13] an increase in venomotor tone and a shift of blood to central veins and heart. However, the increased right atrial pressure does not appear to be the cause of the increased cardiac output but rather may represent a physiological adjustment which maintains cardiac filling at the best possible level during *chronic* reductions in blood volume. Some evidence in support of this interpretation is found in the studies of Sunahara and Beck,[5] who showed that no elevation in right atrial pressure accompanied the increased cardiac output in dogs made anaemic by an acute blood for plasma exchange technique in which little or no reduction in blood volume occurred.

OXYGEN UTILIZATION AND CARDIAC OUTPUT

Normally arterial blood contains about 20 cc. of oxygen/100 cc. blood, almost all of which is in combination with haemoglobin. The arterial haemoglobin is 95 to 97 per cent saturated with oxygen. As the blood traverses the capillary bed, it gives up an average of 5 cc. of oxygen/100 cc. blood (arteriovenous oxygen difference), so that the mixed venous blood in the right heart contains 15 cc. of oxygen/100 cc. of blood. The haemoglobin of mixed venous blood is about 70 per cent saturated with oxygen, and the per cent utilization of arterial oxygen (the ratio, expressed in per cent of the amount abstracted by the tissues to the amount present in arterial blood) is approximately 25 per cent.

In anaemia the haemoglobin level and the oxygen content of arterial blood are reduced in a parallel fashion, whereas the per cent saturation of arterial haemoglobin with oxygen is within normal limits.

At low haemoglobin levels and prior to an increase in cardiac output, the usual tissue uptake of 5 cc. of oxygen/100 cc. blood means that the per cent utilization of arterial oxygen increases, the per cent saturation of mixed venous blood decreases, and tissue oxygen tension falls. Thus, in these circumstances the mechanism of tissue oxygenation is an increased per cent utilization of available oxygen, which continues singly until the haemoglobin reaches some critical level, at which point the cardiac output rises.

The elevated cardiac output is associated with a decreased arteriovenous oxygen difference.[1] Little or none of the increase in cardiac output in uncomplicated anaemia can be attributed to an increased oxygen consumption.[1] Thus, the oxygen saturation of mixed venous blood and tissue oxygen tension, although usually below normal, are increased over that which would occur in the absence of an elevation in cardiac output. Similarly, the increase in per cent utilization of available oxygen is less marked than it would be in the absence of a rise in cardiac output. Thus, eventually, as the anaemia progresses, the burden of oxygen supply to the tissues becomes divided, one part being taken by an increased cardiac output which brings about an increased delivery of oxygen to the tissues and the other part being taken by an increased per cent utilization of available oxygen.

The fact that both the per cent oxygen saturation of mixed venous blood and the tissue oxygen tension is low, when the cardiac output is elevated, has prompted some investigators to suggest a balanced relationship between the degree of tissue anoxia and the degree of elevation in cardiac output.[14] According to this hypothesis, the increased cardiac output occurs in response to the decrease in total peripheral resistance, which in turn results from a direct vasodilating effect of anoxia on peripheral blood vessels.

Some reason to doubt this hypothesis has stemmed from the previously mentioned studies on dogs made anaemic by daily venesections of from 100 to 200 cc./day for 6 to 8 days. After the final venesection the cardiac output rose gradually to reach a maximum over the course of 1 to 7 days, during which time the haemoglobin and blood volume remained unchanged from the levels observed at the end of the bleeding period. Marked tissue anoxia was found at the end of the venesection period and prior to any increase in cardiac output. The total periph-

SECOND WORLD CONGRESS OF CARDIOLOGY — 27TH ANNUAL SCIENTIFIC SESSIONS OF THE A. H. A.

SEPTEMBER 12-17, 1954 — **WASHINGTON, D.C.**

OUTLINE OF SCIENTIFIC PROGRAM — NATIONAL GUARD ARMORY

	SYMPOSIA, ROUND TABLE DISCUSSIONS (PANELS) AND LECTURES MAIN AUDITORIUM — ROOM A	SCIENTIFIC SESSIONS ROOM B	ROOM C	ROOM 12W	ROOM 27E
MON. A.M.	Cardiovascular Epidemiology — Introductory Remarks Paul D. White Atherosclerosis: Ancel Keys, Chairman Other Etiological Factors: Paul D. White, Chairman	Electrocardiography (I)	Drugs and Therapy (I)	Physiology (I)	Occupational Cardiology and Rehabilitation
MON. P.M.	Clinical Value of Instrumental Methods of Diagnosis in Congenital Heart Disease: André Cournand, Chairman Indications for and Results of Operations in Congenital Heart Disease Helen B. Taussig and H. A. Snellen, Chairmen	Coronary Artery Disease	Drugs and Therapy (II)	Physiology (II)	Mitral Stenosis
TUES. A.M.	Rheumatic Fever Research — Experimental Studies on the Nature and Origin of Fibrinoid: Lewis Thomas Diagnosis and Management of Rheumatic Fever and Rheumatic Heart Disease T. Duckett Jones and Maurice Campbell, Chairmen George Brown Memorial Lecture: Alan C. Burton	Pulmonary Heart Disease	Cardiovascular Surgery (I)	Electrocardiography (II)	Arteriosclerosis and Cerebrovascular Disease
TUES. P.M.	Problems of Circulation George E. Burch and Grace M. Roth, Chairmen Prize Lecture of Argentine Society of Cardiology Manuel René Malinow Treatment of Hypertension Eduardo Braun-Menendez and Irvine H. Page, Chairmen	Rheumatic Fever and Rheumatic Heart Disease (I)	Cardiovascular Surgery (II)	Electrocardiography (III)	Ballistocardiography
WED. A.M.	Blood Volume Gustav Nylin and Carl J. Wiggers, Chairmen Physiology of Contractile Protein in Heart Muscle Maurice B. Visscher, Chairman	Rheumatic Fever and Rheumatic Heart Disease (II)	Cardiopulmonary Dynamics	Vectorcardiography*	Congenital Heart Disease (I)
THUR. A.M.	Surgery of Congenital Heart Disease Alfred Blalock and Sir Russell C. Brock, Chairmen Surgery of Non-Congenital Heart Disease Robert E. Gross and Samuel A. Levine, Chairmen	Peripheral Vascular Disease**	Hypertension (I)	Heart Diseases of Uncommon Etiology (I)	Diagnostic Methods
THUR. P.M.	Memorial to Frank Norman Wilson: Louis N. Katz Memorial to Willem Einthoven: H. A. Snellen Electrocardiography Louis N. Katz, Charles E. Kossmann and George E. Burch, Chairmen Ballistocardiography: Isaac Starr, Chairman	Hypertension (II)	Congenital Heart Disease (II)	Heart Diseases of Uncommon Etiology (II)	Phonocardiography and Auscultation
FRI. A.M.	Coronary Heart Disease Howard B. Sprague and Ramón Aixalá, Chairmen Charles Laubry Lecture: Sir John Parkinson Closing Remarks: Charles Laubry and Paul D. White	Subacute Bacterial Endocarditis	Pathology	Diagnostic and Therapeutic Instruments	X-Ray and Angiocardiography

* Special Symposium on Vectorcardiography — THURSDAY A.M., ROOM D George E. Burch, Chairman

** Special Scientific Program — Section on Circulation — THURSDAY P.M., ROOM 201S George E. Burch, A. Wilbur Duryee and Grace M. Roth, Chairmen

SECOND WORLD CONGRESS OF CARDIOLOGY AND THE 27TH ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION, INC.

September 12-17 Washington, D.C.

All those planning to attend the Congress are urged to *submit their applications at the earliest possible date. Any physician may attend the Congress by filling out and sending in the application blank and paying the required registration fee.* Detailed information concerning the Congress is available from the Secretary-General, L. W. Gorham, M.D., Second World Congress of Cardiology, % American Heart Association at 44 East 23rd Street, New York 10, N. Y.

MEMBERSHIP

A registration fee of $25.00 has been established for the combined World Congress and Scientific Sessions. Although registration fees have not been charged professional members of the American Heart Association attending the Annual Scientific Sessions in previous years, the expense of the enlarged and integrated sessions of the forthcoming Congress and the many events associated with it require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events, exhibits and special sightseeing tours in Washington and its environs. Also included are the printed programs, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. *A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns, and nurses.*

SCHEDULE

A tentative schedule of the Congress follows:

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:

9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel

10:30 a.m.: Opening ceremonies at Constitution Hall

8:30 p.m.: Reception for Congress Members, Pan American Building

Monday, Sept. 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory. Sessions will consist of lectures by special invitation, symposia and panel discussions in a large auditorium and presentation of original scientific papers in each of four smaller rooms.

Morning sessions will be held every day from 9:00 a.m. to 12:30 p.m.

Afternoon sessions will be held every day except Wednesday, Sept. 15 and Friday, Sept. 17, from 2:00 p.m. to 5:30 p.m.

Monday, Sept. 13, 8:30 to 10:30 p.m.: Visit to National Gallery of Art, for Congress Members only.

Tuesday, Sept. 14, 8:00 p.m.: Formal banquet for Congress Members, to be held simultaneously at Mayflower and Statler Hotels.

Wednesday, Sept. 15, 2:30 p.m. to 5:30 p.m.: Medical sightseeing tours.

Thursday, Sept. 16, 8:30 p.m.: National Symphony Orchestra Concert.

Friday, Sept. 17, 2:30 to 5:30 p.m.: Medical sightseeing tours.

EXHIBITS

Scientific and industrial exhibits have been planned for the Congress, as well as a motion picture program of professional and scientific films on cardiovascular subjects.

eral resistatnce, however, was not reduced at this time. The total peripheral resistance decreased only as the cardiac output rose, reaching minimal values at the time of the highest cardiac output, at which time tissue anoxia was less marked than at the end of the venesection period. Thus, the direct relationship between tissue anoxia and cardiac output suggested by others would not appear to apply to the period when the cardiac output was increasing to a maximum. Furthermore, when the anaemia was rapidly corrected in dogs[6] and in man[15] by an infusion of concentrated whole blood, the cardiac output did not return to normal levels for several hours. (The dangers of rapid transfusion of anaemic patients, reviewed in the final section, were minimized by the selection of young patients with no other myocardial diseases and by a constant assessment of cardiovascular function.) In these correction experiments despite partial to complete relief of the anoxic stress the total systemic resistance remained low and increased only as the cardiac output decreased towards normal. It was concluded from these studies that tissue anoxia may be the stimulus for the initiation of the elevation in cardiac output, but that it does not appear to be a sustaining factor.

These findings further suggest that the low total peripheral resistance which accompanies the increased cardiac output is not the result of the direct effect of anoxia on peripheral vessels. The decreased total peripheral resistance may result from either a homeostatic mechanism which maintains a near normal blood pressure during the period of cardiac output elevation, or may result from some slowly developed indirect mechanism which dilates peripheral vessels and thus elicits a rise in cardiac output.[14]

The slow appearance of the elevated cardiac output in post-haemorrhagic anaemia has prompted Sharpey-Schafer to suggest that a slow-acting or slowly elaborated humoral mechanism may be involved in this compensation.[3]

The slow rise in cardiac output to a maximum observed in post-haemorrhagic anaemia in dogs as well as the slow return of cardiac output following rapid correction of the anaemia by blood transfusion, also suggests an indirect mechanism, possibly humoral in nature, which is initiated in some way by the stimulus of the low oxygen carrying capacity of the blood.

CLINICAL CONSIDERATIONS

Examination of the patient with severe anaemia reveals signs of a hyperactive circulation. The heart rate is generally increased, and this increased rate undoubtedly contributes to the increased minute output. The apical thrust may be very forceful. The circulation time is shortened. The presence of a decreased blood pressure, widened pulse pressure, and visible capillary pulsations indicate peripheral arteriolar dilatation.

In some severely anaemic patients, when there is an associated malnutrition and wasting, signs of a hyperactive circulation may be absent. In these cases the basal metabolic rate is reduced so that an elevated cardiac output is unnecessary for adequate tissue oxygenation.

The anaemic patient at rest may, through the various adjustments previously described, compensate adequately for the reduced oxygen carrying power of the blood. During exercise, however, symptoms of muscular ischemia (angina or leg cramps) may limit his activity. The development of muscular ischemia is readily understood when one considers the small amount of 'reserve' oxygen in venous blood available for utilization at times of increased activity.

The maintenance of an increased cardiac output, the low oxygen carrying power of blood, and the low 'reserve' oxygen are conditions which favour the development of congestive failure. When congestive failure occurs, signs of a hyperactive circulation may still be present. Similarly, the cardiac output may be still elevated but not adequate when considered in terms of the tissue needs for oxygen or in terms of the level of cardiac output which ordinarily would occur at the existing haemoglobin values. At this time the venous pressure is markedly elevated, and oedema, cardiac enlargement, and electrocardiographic changes are observed. Dyspnoea is not necessarily an indication of congestive failure, for this symptom is seen in uncomplicated anaemia particularly during exertion. Under these circumstances the dyspnoea is referable to the anaemia itself. With the development of congestive failure, however, the severity of the dyspnoea is increased.

The heart in anaemia is working at or near a maximum, and as a result certain dangers attend the transfusion of anaemic patients. Thus, transfusion, when administered too rapidly and in a large volume, may increase the demands placed upon the heart beyond its physiological ability to cope with them. The result is that acute congestive failure and in some instances death may occur. The hazards in the transfusion of the anaemic patient already in congestive failure are obvious. Transfusions, therefore, must be carried out with caution at all times. The use of small volumes of blood administered at slow rates and constant observation of the patient will minimize the risk. These precautions are particularly necessary in the older age group where other myocardial diseases may be present.

SUMMARY

The haemoglobin level at which an elevation in cardiac output occurs appears to be determined, at least in part, by the rate at which anaemia develops or by the accompanying level of the blood volume.

At reduced haemoglobin levels and prior to the elevation in cardiac output, the tissue oxygen supply is maintained by an increased per cent utilization of arterial oxygen.

An increased right atrial pressure is found in association with the increased cardiac output and reduced blood volume in chronic and post-haemorrhagic anaemia. The increased atrial pressure does not appear to be the cause of the elevated cardiac output but rather may represent a physiological mechanism which brings about a shift of blood to the central veins and heart, thus maintaining cardiac filling during chronic reductions in blood volume.

There is no unanimity in findings to support the concept of a balanced relationship between cardiac output and tissue oxygen tension. It is suggested that tissue anoxia may be the stimulus for the initiation of the increase in cardiac output, but it would not appear to be a sustaining factor.

Indirect evidence suggests that the increased cardiac output may be the result of a humoral mechanism initiated in some way by the stimulus of a decreased tissue oxygen tension.

The clinical manifestations referable to the cardiovascular system are briefly reviewed, and the dangers of blood transfusion are discussed.

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The opinions and conclusions expressed herein are those of the author and do not necessarily represent the official views of the Scientific Council of the American Heart Association.